Minimal Residual Disease (MRD) as a Surrogate Enpoint in Acute Lymphoblastic Leukemia (ALL) Workshop

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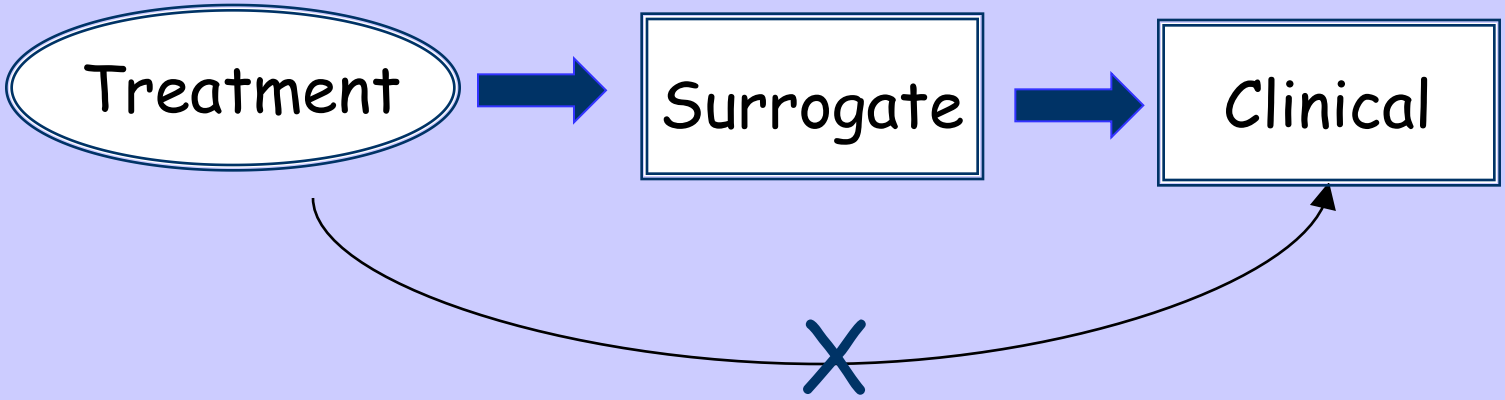
Validation of a surrogate marker

a surrogate marker is treatment (class) specific and needs to be validated for that treatment (class)
This is generally done with a meta-analysis of randomized trials



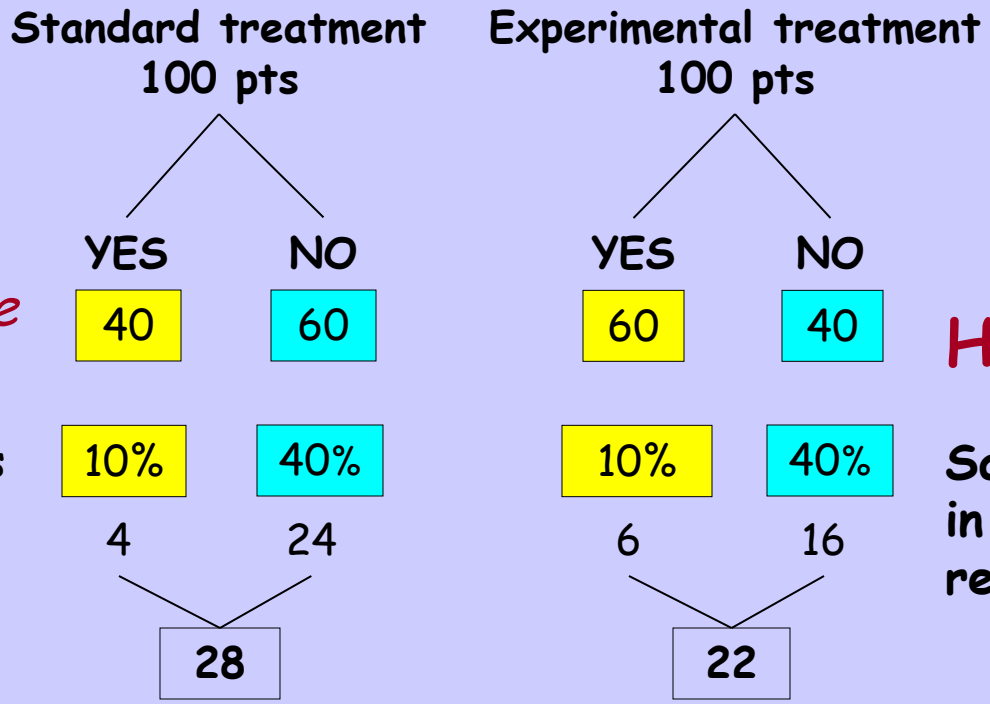
MRD in ALL can be used as a surrogate?

- MRD is a strong prognostic factor for established clinical end-points (EFS).
  - Of note, this holds true also when MRD is used for patients stratification, i.e. for tayloring treatment intensity
- MRD captures fully the treatment effect on the clinical end-point.

  This is not proved yet (for any class of drugs)
- Could it be easier to prove surrogacy for targeted drugs (ex. TKI inhibitors) ?

Scenario 1

Perfect Surrogate



High activity

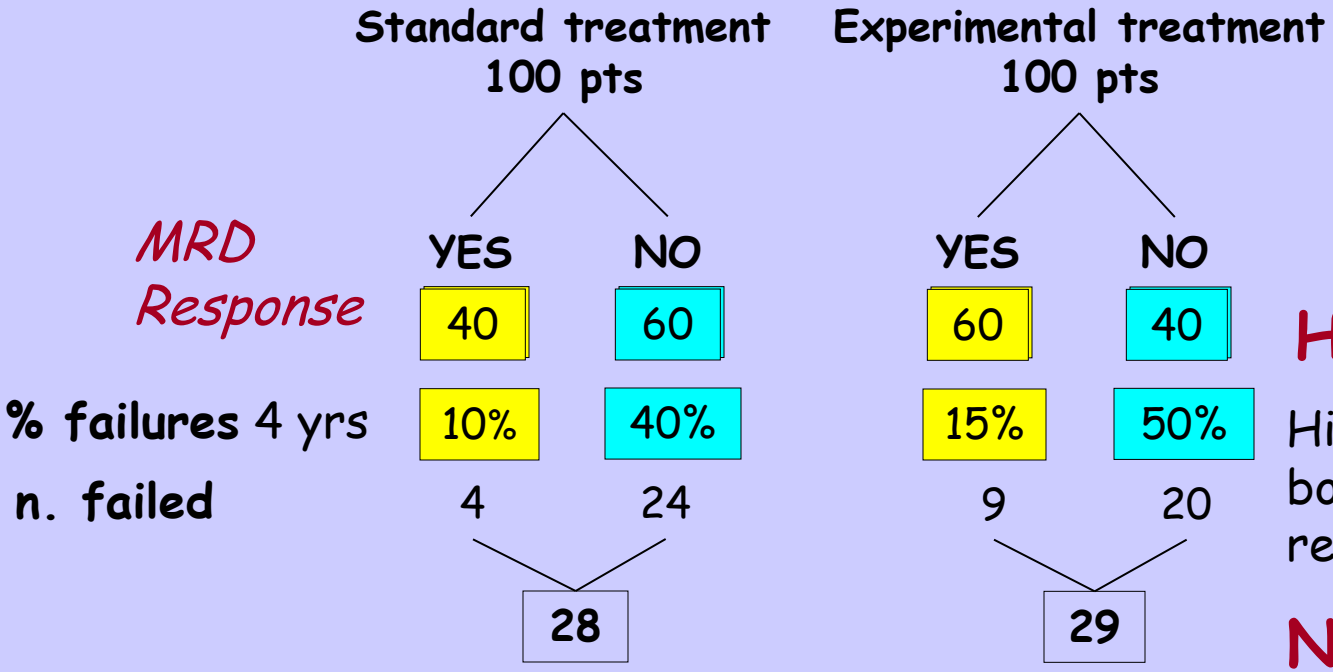
Same rate of failure in responders/non responders

Modest effect on clinical outcome

Scenario 2

Not strictly a valid Surrogate

The same benefit on response (20% increase) translates in NO clinical benefit because the higher response level in the experimental arm carries a higher failure rate in both responders and non responders (which lost pts at better prognosis)



High activity

Higher failure rate in both responders and non responders

No clinical benefit

How to define response in ALL in terms of MRD levels ?

- Define a cut-point that strongly discriminates prognosis?

  I.e. responders are

  "negative" or

  MRD< 1x10-4?

  The methodology used for measuring MRD is very relevant for comparability between studies

At which time point should MRD be measured?

An early time point is usually preferred.

Advantages:

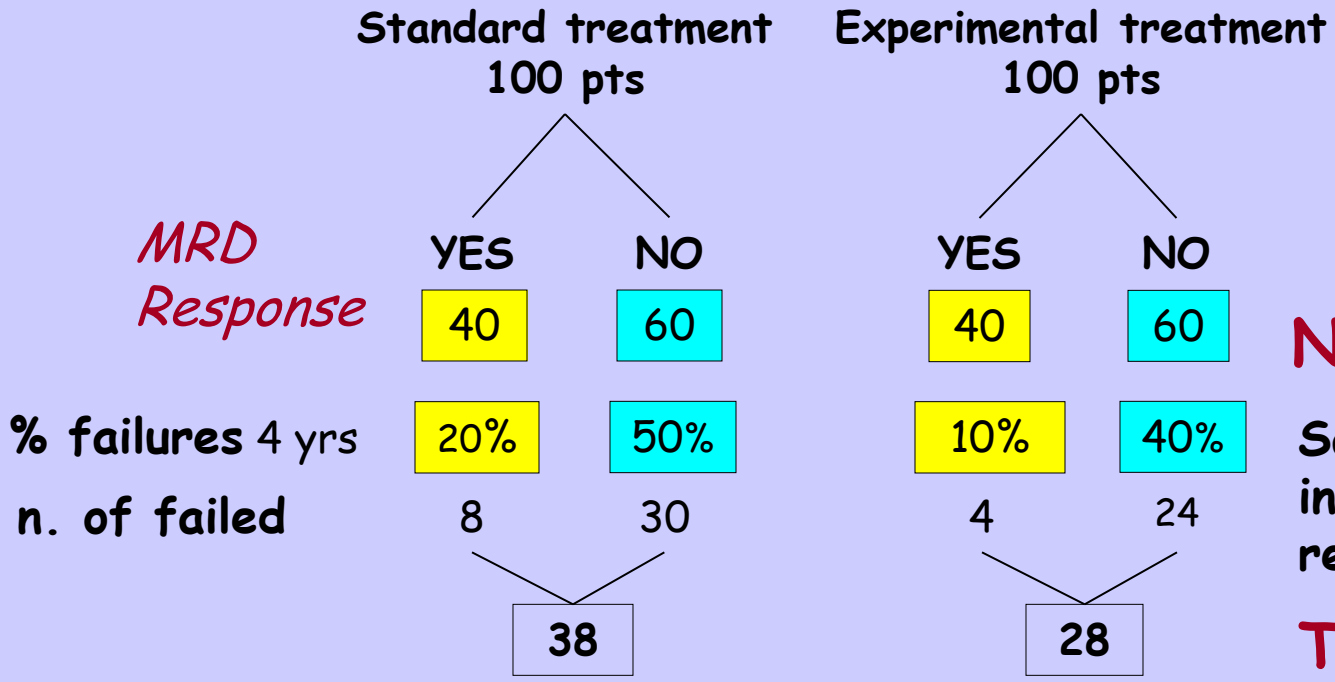
- results in short time
- disease levels still heterogeneous (negative for the majority of patients after the first 3-4 months of treatment);
- in high risk subgroups, where relapses occur relatively early, an early time point might be predictive of relapse

Disadvantages:

- limits research to treatments used in early phases
- in the majority of ALL patients, where relapses occur late after the end of therapies, an early time point might be poorly predictive

Scenario 3

Not a Surrogate



NO activity

Same rate of failure in responders/non responders

There is effect on clinical outcome

MRD is not a surrogate, yet it is a strong prognostic factor (30% difference in failure rate between responders and non responders) and treatment has an effect on outcome

Criteria for Validation (Prentice)

1. Treatment affects the surrogate
2. Treatment affects the clinical end-point
3. Surrogate and clinical end-point are "correlated"
4. Treatment effect disappears when adjusted by the surrogate